REMARKS/ARGUMENTS

The Office Action, dated March 11, 2003, has been carefully considered. Claims 1, 4-23 and 25-42 are pending and under examination. The claims have been amended to more clearly set forth the Applicants' contributions to the art and do not introduce new matter into the disclosure of the invention. It is believed that no additional fee is required as the number of independent and dependent claims is the same as originally filed.

Applicants note Examiner's comments that the page and line numbers made reference to in Applicants' previous response do not fully correlate with the instant specification. Applicants regret this error and have tried to provide correct page and line numbering corresponding to the application, as filed. Additionally, Applicants appreciate Examiner's withdrawal of claim rejections under 35 USC 112/103.

New Grounds of Rejection Under 35 USC 112

Under Section 3 of the detailed action, the Examiner has rejected claims 1, 4-23 and 25-42 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends that claim 1, step i), is vague and indefinite in reciting "wherein the target analytes is ... peptide or protein hormone or cytokine" because the method is drawn to measuring the production of secreted analyte as required by the preamble. Applicants intend that the target analytes is always a secreted peptide or secreted protein and not directed to intracellular proteins. Claim 1 has now been amended to more clearly set forth the nature of the invention as providing for measuring only *secreted* analytes. Support may be found on page 19, lines 8 and 13-15, and page 21, lines 6-8, where the specification describes that this technique can be used to measure molecules other than cytokines, that are secreted, shed, or otherwise produced in vivo, including, but not limited to, hormones, peptides, and drug metabolism products.

The Examiner contends that claim 20 as indefinite in reciting "wherein the second targeting moiety binds specifically to the first targeting moiety, wherein the second targeting moiety is injected in sufficient quantity that a measurable fraction of first targeting moiety is bound by the second targeting moiety" because it is unclear what structural and functional cooperative relationship exists between the second targeting moiety and the desired target analytes. Claim 20 is an alternative method to that recited in claim 1. Claim 20 provides for the additional steps of (i) contacting the assay mixture after step (e) and before step (f) in claim 1 with a detectable anti-ligand binding partner that is complementary to the targeting moiety, either the targeting moiety itself or a ligand label operatively linked to the targeting moiety; (ii) detecting the amount of detectable anti-ligand binding partner after washing; and (iii) correlating the detected amount of detectable anti-ligand binding partner to the amount of targeting moiety:target analyte:capture moiety complexes in the assay mixture; wherein the amount of targeting moiety:target analyte:capture moiety complexes detected provides a measure of the production of secreted target analyte during the defined period of time. Support for this amendment can be found on page 13, lines 1-7 and 13-15, page 15, lines 13-15, page 17, lines 17-23 and page 18, lines 1-2, where the specification clearly describes the use of ligand/anti-ligand pairs as a complementary set of molecules acting as a detection assay.

The Examiner contends that claim 25 remains confusing in reciting "the means for detecting the ... complexes" because the term "means" implies an element or apparatus rather than an assay. Claim 25 has now been amended to provide that the complexes are detected by radioimmunoassay, as recommended by the Examiner.

The Examiner contends that claim 31 remains confusing in reciting "capture moiety is labeled by linking to a fluorescent labeling compound." Claim 31 has now been amended to provide that the "capture moiety is labeled with a fluorescent label".

The Examiner contends that claim 34 remains confusing in reciting "the label is an enzyme indicating means operatively linked to the targeting moiety" because the term "means" implies an element or and apparatus accompanying the enzyme. Claim 34 has now been

amended to provide that the label is "an enzyme that is operatively linked to the targeting moiety." Furthermore, the Examiner contends that claim 34 is vague and indefinite in reciting " the second reagent comprises a capture moiety specific for the target analyte even when such target analyte is conjugated with the labeled targeting moiety" because, as stated by the Examiner, it appears that in order to be useful in detecting the presence of analyte as recited in claim 1, the capture moiety is required to capture the target analyte that is conjugated with the labeled targeting moiety thus forming the necessary complexes. In order to prevent any ambiguities, claim 34 has now been placed into independent form. Furthermore, claim 34 has now been further amended to provide that the second reagent comprises "a capture moiety specific for binding the target analyte at a binding site different from that for the labeled targeting moiety so that the binding of the analyte by the capture moiety may form a labeled targeting moiety:target analyte:capture moiety complex." Support for this can be found on page 19, lines 18-22.

The Examiner contends that claim 37 remains indefinite, confusing, and inconsistent in relation to claim 20 from which it depends in reciting " having first targeting moieties ... that immunoreacts with a target analyte ... in having second targeting moieties that immunoreacts with the target analyte at a site different from the first targeting moieties" because claim 20 recites that "the second targeting moiety binds specifically to the first targeting moiety and not the target analyte at a different site from the first targeting moieties." In order to prevent any ambiguities, claim 37 has now been placed into independent form. Furthermore, claim 37 has now been further amended to provide for (a) labeled first targeting moieties that immunoreact with a target analyte, (b) second targeting moieties that immunoreact with the label of the first targeting moieties; and (c) a capture moieties specific for the target analyte, wherein the capture moiety is specific for a determinant site on the analyte different from the determinant site recognized by the targeting moiety so that the binding of the analyte by the capture moiety will not be inhibited by the binding of the analyte by the labeled targeting moiety that had been

injected into the animal or human. Support for this can be found on page 19, lines 18-22 and page 30, lines 6-7.

New Matter. Rejections Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claims 1, 4-23 and 25-42 under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner contends that the specification does not provide any literal support for the recitation of "the targeting moiety is injected in sufficient quantity that a measurable fraction of target analyte is bound by the labeled neutralizing targeting moiety" in claim 1. Therefore, the Examiner contends that this limitation constitutes new matter. Applicants respectfully point out that antecedent basis may be found on page 19, lines 7-12, wherein the specification provides that the targeting moiety needs to be injected in sufficient quantity that a measurable fraction of secreted analyte is bound by the [targeting moiety]; and must have a sufficient avidity for the analyte that much of the analyte bound by the [targeting moiety] will remain bound in vehicle by the [targeting moiety] for a period of hours to days, and during a subsequent *in vitro* assay." Applicants believe no amendment is necessary.

Furthermore, the Examiner contends that the specification does not provide literal support for the recitation of "obtaining a sample ... after a defined period of time" which is "from about one hour to 72 hours" in claims 1 and 14, respectively. Therefore, the Examiner contends that this limitation constitutes new matter. Applicants respectfully point out that antecedent basis may be found on page 17, lines 9-10, wherein the specification states that "After a set period of time, typically from about 1 hour to about 72 hours, a blood sample is taken from the host and serum prepared." Applicants believe no amendment is necessary.

The Examiner has further rejected claims 1, 4-23 and 25-42 under 35 U.S.C. 112, first paragraph contending that these claims, while being enabled for *in vivo* targeting, *in vivo*

capturing, and measuring production of secreted cytokines, secreted peptides and protein hormones in the blood, does not reasonably provide for enablement of *in vivo* targeting, *in vitro* capturing, and measuring of any other peptide, protein, or cytokine, *i.e.* intracellular, in the peripheral blood. The Examiner points out that the present claims broadly recites a method for measuring the *in vivo* production of any and all peptides or protein hormones, regardless of where or how they are produced.

Applicants have now amended the claims to provide for only the measurement of *secreted* target analyte wherein the secreted target analyte is a cytokine, peptide or protein hormone, as detailed above.

Response to Arguments

The Examiner has, upon further consideration, made a new ground of rejection in view of an amendment made to independent claim 1, step i), "wherein the target analyte is a secreted cytokine, peptide, protein hormone, or cytokine." The Examiner points out that while the claims are enabled for secreted cytokines which are functionalized peptides, secreted peptides and secreted protein hormones, they are not enabled for any other cytokine, *i.e.*, intracellular, or any other endogenous non-circulating peptide or protein hormone.

As noted above, Applicants intend that the target analytes is always a secreted peptide or secreted protein and not directed to intracellular proteins. Claim 1 has now been amended to more clearly set forth the nature of the invention as providing for measuring only *secreted* analytes. Support may be found on page 19, lines 8 and 13-15, and page 21, lines 6-8, where the specification describes that this technique can be used to measure molecules other than cytokines, that are secreted, shed, or otherwise produced in vivo, including, but not limited to, hormones, peptides, and drug metabolism products.

In view of the above, it is respectfully submitted that the claims as amended and presented before the Examiner are in condition for allowance. Accordingly, reconsideration and

withdrawal of the rejections are requested and allowance of claims 1, 4-23 and 25-42 is earnestly solicited.

The Assistant Commissioner for Patents is authorized to charge any deficiency or credit any overpayment to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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